

WHAT IS CLAIMED IS

1. A compound of formula (I)



(I),

5 or a therapeutically acceptable salt thereof, wherein

A_0 is absent or selected from the group consisting of N-acetyl, N-acetylazetidine-2-carbonyl, N-acetylazetidine-3-carbonyl, N-acetylhippocotyl, N-acetylpyrrolidine-4-acetyl, and N-acetylprolyl;

10 A_1 is selected from the group consisting of D-alanyl, (1R,3S)-1-aminocyclopentane-3-carbonyl, (1S,4R)-1-aminocyclopent-2-ene-4-carbonyl, 1-amino-1-cyclopropanecarbonyl, 3-(4-chlorophenyl)alanyl, 4-hydroxyprolyl, N-methylnorvalyl, 3-(4-methylphenyl)alanyl, N-methylprolyl, N-methylthreonyl(benzyl), norleucyl, propargylglycyl, sarcosyl, and (2,3,5,6-tetrahydro-1-thiopyran-4-yl)glycyl;

15 A_2 is selected from the group consisting of [(1S,3R)-1-aminocyclopentane-3-carbonyl], [(1R,4S)-1-aminocyclopent-2-ene-4-carbonyl], [(1S,4R)-1-aminocyclopent-2-ene-4-carbonyl], asparaginy, 3-(3-cyanophenyl)alanyl, 3-(4-cyanophenyl)alanyl, 3-(3,4-dimethoxyphenyl)alanyl, 3-(4-fluorophenyl)alanyl, 3-(2-furyl)alanyl, glutaminy, glycyl, 3-(4-methylphenyl)alanyl, norvalyl, and 3-(thiazol-5-yl)alanyl;

20 A_3 is selected from the group consisting of asparaginy, glutaminy, isoleucyl, and valyl;

A_4 is selected from the group consisting of D-alloisoleucyl, D-isoleucyl, D-leucyl, and D-penicillaminy(S-methyl);

A_5 is selected from the group consisting of allothreonyl, aspartyl, 4-hydroxyprolyl, seryl, threonyl, and threonyl(O-acetyl);

25 A_6 is selected from the group consisting of allothreonyl, glutaminy, 4-hydroxyprolyl, norvalyl, ornithyl(N-delta-acetyl), prolyl, seryl, and tryptyl;

A_7 is selected from the group consisting of isoleucyl, D-isoleucyl, and prolyl;

A_8 is selected from the group consisting of arginy, glutaminy, and ornithyl;

A_9 is prolyl; and

30 A_{10} is selected from the group consisting of D-alanylamide, D-lysyl(N-epsilon-acetyl)amide, ethylamide, and N-methyl-D-alanylamide;

provided that when A_0 is absent A_1 is N-methylprolyl; and

35 provided that when A_1 is sarcosyl A_0 is not acetyl; or A_2 is not asparaginy, glutaminy, or glycyl; or A_4 is not D-alloisoleucyl, D-isoleucyl, or D-leucyl; or A_5 is not allothreonyl, seryl, or threonyl; or A_6 is not glutaminy, norvalyl, seryl, or tryptyl; or A_8 is not arginy; or A_{10} is not D-alanylamide or ethylamide.

2. A compound according to Claim 1 wherein A₀ is absent.
3. A compound according to Claim 2 wherein A₄ is D-alloisoleucyl.
4. A compound according to Claim 3 selected from the group consisting of
N-MePro-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Gln-D-alloIle-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂;
N-MePro-Gly-Val-D-alloIle-Ser-Ser-Ile-Arg-ProNHCH₂CH₃; and
5 N-MePro-Gly-Val-D-alloIle-Thr-Trp-Ile-Arg-ProNHCH₂CH₃.
5. A compound according to Claim 2 wherein A₄ is D-leucyl.
6. A compound according to Claim 5 selected from the group consisting of
N-MePro-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃; and
N-MePro-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂.
7. A compound according to Claim 2 wherein A₄ is D-isoleucyl.
8. A compound according to Claim 7 wherein A₅ is allothreonyl.
9. A compound according to Claim 8 selected from the group consisting of
N-MePro-Gly-Val-D-Ile-alloThr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-Ile-alloThr-Gln-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-Ile-alloThr-Nva-Ile-Arg-Pro-D-AlaNH₂;
5 N-MePro-Gly-Val-D-Ile-alloThr-Ser-Ile-Arg-ProNHCH₂CH₃; and
N-MePro-Gly-Val-D-Ile-alloThr-Nva-Pro-Arg-ProNHCH₂CH₃.
10. A compound according to Claim 7 wherein A₅ is threonyl.
11. A compound according to Claim 10 selected from the group consisting of
N-MePro-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Gln-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
5 N-MePro-Gly-Val-D-Ile-Thr-Nva-D-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Gln-D-Ile-Thr-Nva-D-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Gln-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂;
N-MePro-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂;

- N-MePro-Gly-Ile-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Asn-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gln-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gln-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂;
N-MePro-Gly-Val-D-Ile-Thr-alloThr-Ile-Arg-ProNHCH₂CH₃; and
N-MePro-Gly-Val-D-Ile-Thr-Gln-D-Ile-Arg-ProNHCH₂CH₃.
12. A compound according to Claim 1 wherein A₀ is N-acetylnipecotyl.
13. A compound according to Claim 12 which is
N-(N-acetylnipecotyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃.
14. A compound according to Claim 1 wherein A₀ is N-acetylpiperidine-4-acetyl.
15. A compound according to Claim 14 which is
N-[2-(N-acetylpiperidine-4-acetyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃].
16. A compound according to Claim 1 wherein A₀ is N-acetylprolyl.
17. A compound according to Claim 16 which is
N-Ac-Pro-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃.
18. A compound according to Claim 1 wherein A₀ is N-acetylazetidine-2-carbonyl.
19. A compound according to Claim 18 which is
N-[(N-acetylazetidine-2-carbonyl)]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃.
20. A compound according to Claim 1 wherein A₀ is N-acetylazetidine-3-carbonyl.
21. A compound according to Claim 20 which is
N-[(N-acetylazetidine-3-carbonyl)]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃.
22. A compound according to Claim 1 wherein A₀ is acetyl.

23. A compound according to Claim 22 wherein A₄ is D-penicillaminyl(S-methyl).
24. A compound according to Claim 23 selected from the group consisting of
N-Ac-Sar-Gly-Val-D-Pen(SMe)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-Ac-Sar-Gly-Val-D-Pen(SMe)-Ser-Nva-Ile-Arg-ProNHCH₂CH₃;
N-Ac-Sar-Gly-Val-D-Pen(SMe)-Thr-Gln-Ile-Arg-ProNHCH₂CH₃;
5 N-Ac-Sar-Gly-Gln-D-Pen(SMe)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃; and
N-Ac-Sar-Gly-Asn-D-Pen(SMe)-Thr-Nva-Ile-Arg-ProNHCH₂CH₃.
25. A compound according to Claim 22 wherein A₄ is D-alloisoleucyl.
26. A compound according to Claim 25 selected from the group consisting of
N-Ac-Sar-(4-CN)Phe-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-Ac-Sar-(4-F)Phe-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-Ac-Sar-(4-Me)Phe-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-Ac-Sar-Gly-Val-D-alloIle-Hyp-Nva-Ile-Arg-ProNHCH₂CH₃; and
N-Ac-Sar-Gly-Val-D-alloIle-Thr-Hyp-Ile-Arg-ProNHCH₂CH₃.
27. A compound according to Claim 22 wherein A₄ is D-leucyl.
28. A compound according to Claim 27 selected from the group consisting of
N-Ac-Sar-(3-CN)Phe-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-[(1S,4R)-1-N-acetylaminocyclopent-2-ene-4-carbonyl]-Gly-Val-D-Leu-Thr-Nva-
Ile-Arg-ProNHCH₂CH₃;
5 N-[(1R,3S)-1-N-acetylaminocyclopentane-3-carbonyl]-Gly-Val-D-Leu-Thr-Nva-Ile-
Arg-ProNHCH₂CH₃;
N-Ac-(4-Me)Phe-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-(1-N-acetylamino-1-cyclopropanecarbonyl)-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-
ProNHCH₂CH₃;
10 N-Ac-(2,3,5,6-Tetrahydro-1-thiopyran-4-yl)gly-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-
ProNHCH₂CH₃;
N-Ac-Hyp-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-Ac-Nle-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-Ac-(4-Cl)Phe-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
15 N-Ac-propargylgly-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃; and
N-Ac-D-Ala-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃.

29. A compound according to Claim 22 wherein A₄ is D-isoleucyl.

30. A compound according to Claim 29 selected from the group consisting of

N-Ac-Sar-Gly-Val-D-Ile-Asp-Nva-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-Taz-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-(3,4-diMeO)Phe-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-(2-furyl)Ala-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-[(1S,3R)-1-aminocyclopentane-3-carbonyl]-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-[(1R,4S)-1-aminocyclopent-2-ene-4-carbonyl]-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-[(1S,4R)-1-aminocyclopent-2-ene-4-carbonyl]-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-Gly-Val-D-Ile-alloThr-Pro-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-Nva-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-Asn-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Orn-ProNHCH₂CH₃;

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Gln-ProNHCH₂CH₃;

N-Ac-Sar-Gly-Val-D-Ile-Thr(OAc)-Orn(N-delta-Ac)-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-NMe-D-AlaNH₂;

N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-Lys(Ac)NH₂;

N-Ac-N-MeNva-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃; and

N-Ac-N-MeThr(Bzl)-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃.

31. A pharmaceutical composition comprising a compound of formula (I) or a therapeutically acceptable salt thereof, in combination with a therapeutically acceptable carrier.

32. A method of inhibiting angiogenesis in a mammal in recognized need of such treatment comprising administering to the mammal a therapeutically acceptable amount of a compound of formula (I), or a therapeutically acceptable salt thereof.

33. A compound selected from the group consisting of

N-(N-acetyl nipecotyl)-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

N-[N-acetyl piperidine-4-acetyl]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Pro-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

N-Ac-Sar-(4-CN)Phe-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;

- 45 N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Orn-ProNHCH₂CH₃;
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Gln-ProNHCH₂CH₃;
N-Ac-Sar-Gly-Val-D-Ile-Thr(OAc)-Orn(N-delta-Ac)-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-Leu-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-Ile-Thr-Gln-Ile-Arg-ProNHCH₂CH₃;
50 N-MePro-Gly-Gln-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-Ile-Thr-Nva-D-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Gln-D-Ile-Thr-Nva-D-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-Ile-alloThr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Gln-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂;
55 N-MePro-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂;
N-MePro-Gly-Gln-D-alloIle-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂;
N-MePro-Gly-Ile-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-alloIle-Ser-Ser-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Asn-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gln-Val-D-Ile-Thr-Nva-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gln-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-AlaNH₂;
N-MePro-Gly-Val-D-Ile-alloThr-Gln-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-Ile-alloThr-Nva-Ile-Arg-Pro-D-AlaNH₂;
N-MePro-Gly-Val-D-Leu-Ser-Nva-Ile-Arg-Pro-D-AlaNH₂;
N-MePro-Gly-Val-D-Ile-alloThr-Ser-Ile-Arg-ProNHCH₂CH₃;
N-MePro-Gly-Val-D-Ile-Thr-alloThr-Ile-Arg-ProNHCH₂CH₃;
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-NMe-D-AlaNH₂;
N-[(N-acetylazetidine-2-carbonyl)]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-
ProNHCH₂CH₃;
70 N-[(N-acetylazetidine-3-carbonyl)]-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-
ProNHCH₂CH₃; and
N-Ac-Sar-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-D-Lys(Ac)NH₂.